known, as demonstrated by randomly selected abstracts obtained by a search of the National Library of Medicine data base, copies of which are enclosed. Applicant is not claiming the tumor vaccines per se, except in combination with the ultrafiltration system defined by claim 1. Note that this is consistent with the Examiner's own position, stated at the bottom of page 5 to the top of page 6 of the office action.

Claims 10-14, 17 and 23 have been clarified as suggested by the examiner.

Rejections under 35 U.S.C. §103(a)

Claims 1-4, 8, 9, 16, 18-20, and 22 were rejected under 35 U.S.C. §103(a) over U.S. Patent No. 4,708,713 to Lentz. Claim 21 was rejected under §103 as obvious over Lentz in combination with U.S. Patent No. 5,523,096 to Okarma, et al. Claims 5, 6, 10-15, 17, and 23 were rejected under §103 as obvious over Lentz in combination U.S. Patent 5,861,483 to 5,861,483 to Wolpe. Claim 7 was rejected under §103 as obvious over Lentz in combination with Chen, et al., J. Neuropath. Exper. Neurol. 56(5), 541-550 (1997). These rejections are respectfully traversed.

The Invention

The invention is the discovery that one can selectively remove molecules of less than 120,000 daltons from the blood of a patient and induce remission in a cancer or other types of chronic disease, and that this process, in combination with certain adjuvant therapies, can not only induce a remission, but maintain the patient in remission. This discovery is very important to the clinical use of this treatment since it allows the patient to retain their immunoglobulins, thereby enhancing the patient's ability to mount an effective immune response after ultrapheresis. With the prior art filter, essentially all of the immunoglobulins as well as albumin is removed from the blood by the filtration process. This necessitated administration of plasma

rather than just albumin following ultrapheresis, increasing the cost as well as the risk of infection associated with multiple transfusions.

The examples are of actual cancer patients who had failed all conventional therapies. These were all terminal patients whose tumors were resistant to chemotherapy and radiation alone, but which went into remission and were maintained in remission using the ultrapheresis followed by a therapy such as with an anti-angiogenesis inhibitor. The results are significantly better than those obtained using ultrapheresis alone.

Lentz

The Lentz patent was filed a number of years ago. The molecular weight cutoff described in the patent is substantially higher than the claimed limitation, greater than 200,000, see col. 6, lines 34-46.

There is nothing in Lentz that would lead one skilled in the art to believe that the cutoff could be decreased in size, allowing molecules between 120,000 and 200,000 daltons in molecular weight to be retained, including the majority of the immunoglobulins, since there is no disclosure of the mechanism of action nor what was being removed by the filter, that was leading to cancer remission. In fact, col. 6, lines 44-46, would lead one skilled in the art away from the claimed method since it makes it clear that it was believed that there was a higher molecular weight complex that might be involved in preventing the body from killing the tumor - even more of this inhibitory material would be retained by the filter having a decreased molecular weight cutoff. Moreover, if it was immunoglobulins that were protecting the tumor from the host, lowering the molecular weight cutoff would have made the method completely ineffective.

In summary, Lentz discloses only that removal of blood components having a molecular weigh of less than 200,000 daltons can cause cancer remission. Not only is there no mechanism

disclosed that would lead one to believe it was the lower molecular weight components that were critical to the process, but the patent actually teaches away from going to a lower molecular weight cutoff. It was only by actually testing patients to determine if the method would be — What?

Chen, et al.

Chen et al., describes the production by tumor cells in cell culture of TNF- receptors, which "may play a role in the mechanism by which malignant gliomas downregulate the effects of infiltrating immune-competent cells." (Abstract, last line). The language at page 545 is even less certain, "Shed receptors consist of the extracellular components of the transmembrane TNFR, and may play a physiological role in mitigating the systemic effects of TNF." The authors conclude at page 549 that additional studies relating to the interactions of these molecules and cytokines to determine their roles are underway.

If all of the possible mechanisms proposed based on studies in cell culture had proven useful, the claimed method would no longer be needed. There is nothing in this application that leads one skilled in the art to say that removal of the receptors alone will be sufficient to induce cancer. There is certainly nothing that would lead one skilled in the art to combine a selective removal of these inhibitors using filtration or chromatography, with a reasonable expectation of success.

35 U.S.C. §103 requires that the prior art not only disclose the claimed elements, but lead one skilled in the art to combine them as applicants have done, with a reasonable expectation that the combination will be effective for the desired purpose. Nothing in Lentz nor Chen suggests the combination, nor creates an expectation of success.

Okarma, et al.

Okarma, et al., describes removal of cytokines, but makes no mention of cytokine

inhibitors. Okarma, et al., teaches away from removal of other blood components, but stating that removal of the cytokines alone is sufficient to treat the patient.

Therefore, there is nothing that would lead one to combine Okarma, et al., with Lentz, modify Lentz to remove lower molecular weight blood components, modify Okarma et al., to leave in the cytokines but remove the cytokine inhibitors, and have any expectation of success.

Wolpe, et al.

Wolpe, et al., states at col. 2, lines 25-45, that "an effective stem cell inhibitor would protect these cells and allow for the optimization of these therapeutic regimens. Just as there is a proven need for a variety of stimulatory cytokines.. depending upon the clinical situation, so too it is likely that a variety of inhibitory factors will be needed to address divergent clinical needs."

One is hard pressed how this can be interpreted to state that one should combine a treatment wherein blood components of less than 120,000 daltons (which would typically remove most of the same things that Wolpe says are needed), then combine that therapy with another treatment which could be anyone of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, and radiation, in a dosage formulation for treatment of the patient following ultrapheresis.

Even less apparent is that one would obtain the significantly better results obtained using the combination, as demonstrated by the examples. In fact, these patients had all been treated with radiation and chemotherapy and had FAILED the treatments. The combination of these therapies with ultrapheresis would at best have been predicted to be no different than the result using ultrapheresis alone. In fact, better results were obtained than with either alone. This simply could not have been predicted from Lentz, Wolpe, or the combination thereof.

Summary

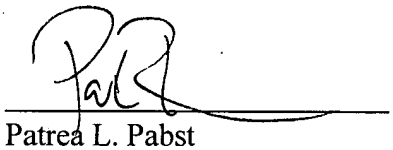
None of the art, alone or in combination, discloses all of the claimed elements.

None of the art, alone or in combination, provides the motivation to combine what is disclosed in the art, and modify as applicant has done, either as to the molecular weight cutoff of the filter alone, or the combination of the filter with another treatment such as administration of anti-angiogenic compounds, procoagulant compounds, cytokines, chemotherapeutic agents, or radiation, in a dosage formulation for treatment of the patient.

None of the art, alone or in combination, leads one skilled in the art to predict that the combination would be more effective than either treatment alone.

Allowance of all claims 1-23, as amended, is earnestly solicited. A copy of all claims as amended is attached in an appendix to facilitate the examiner's review.

Respectfully submitted,



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